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The effect of cannabidiol (CBD) on simulated car driving performance: A randomised, double-blind, placebo-controlled, crossover, dose-ranging clinical trial protocol.

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Key Words: cannabidiol; driving simulation; cognition; psychomotor; mobile drug testing; medicinal cannabis.

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The effect of cannabidiol (CBD) on simulated car driving performance: A randomised, double-blind, placebo-controlled, crossover, dose-ranging clinical trial protocol.

Abstract

Objective: Interest in the use of cannabidiol (CBD) is increasing worldwide as its therapeutic effects are established and legal restrictions moderated. Unlike Δ^9 -tetrahydrocannabinol (Δ^9 -THC), CBD does not appear to cause cognitive or psychomotor impairment. However, further assessment of its effects on cognitively demanding day-to-day activities, such as driving, is warranted. Here, we describe a study investigating the effects of CBD on simulated driving and cognitive performance. **Methods:** 30 healthy individuals will be recruited to participate in this randomised, double-blind, placebo-controlled crossover trial. Participants will complete four research sessions each involving two 30-minute simulated driving performance tests completed 45- and 210-minutes following oral ingestion of placebo, or 15, 300, or 1500 mg CBD. Cognitive function and subjective drug effects will be measured, and blood and oral fluid sampled, at regular intervals. Oral fluid drug testing will be performed using the Securetec DrugWipe[®] 5S and Dräger DrugTest[®] 5000 devices to determine whether CBD increases the risk of “false-positive” roadside tests to Δ^9 -THC. Non-inferiority analyses will test the hypothesis that CBD is no more impairing than placebo. **Conclusion:** This study will clarify the risks involved in driving following CBD use and assist in ensuring the safe use of CBD by drivers.

Key Words: cannabidiol; driving simulation; cognition; psychomotor; mobile drug testing; medicinal cannabis.

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1.0 Introduction

Evidence supporting the therapeutic use of cannabis and its isolated cannabinoid constituents (e.g. Δ^9 -tetrahydrocannabinol [Δ^9 -THC], cannabidiol [CBD]) has strengthened in recent years (National Academies of Sciences Engineering and Medicine, 2017). CBD is of particular interest given its minimal side effects (Bergamaschi *et al.*, 2011a; Taylor *et al.*, 2018) and potential as an anti-inflammatory, neuroprotective and analgesic agent (Pisanti *et al.*, 2017). Several clinical studies have also observed anxiolytic (e.g. 300–600 mg CBD, oral [p.o.]) (Bergamaschi *et al.*, 2011b; Crippa *et al.*, 2011; Linares *et al.*, 2019; Zuardi *et al.*, 1993), anti-psychotic (e.g. 600–1280 mg CBD·d⁻¹, p.o.) (Boggs *et al.*, 2018b; Leweke *et al.*, 2012; McGuire *et al.*, 2018; Zuardi *et al.*, 2009) and anticonvulsant (e.g. 5–20 mg CBD·kg⁻¹·d⁻¹, p.o.) (Devinsky *et al.*, 2017; Devinsky *et al.*, 2018; Thiele *et al.*, 2018) effects, with the Food and Drug Administration recently approving the oral CBD solution, *Epidiolex*[®], for the treatment of seizures associated with intractable epilepsy (Chen, Borgelt, & Blackmer, 2019).

As well as becoming more readily available to certain clinical populations, the introduction of over-the-counter CBD-containing “nutraceuticals” in many countries has resulted in CBD also being more accessible to the general public. These products are typically marketed as “health-promoting” and contain relatively small amounts of CBD (e.g. ~10–20 mg·mL⁻¹) (Bonn-Miller *et al.*, 2017). Given its ready availability and therapeutic potential, it is likely that CBD use will become more widespread in the coming years (Leas *et al.*, 2019). While CBD is reported to be safe and well-tolerated in humans (Bergamaschi *et al.*, 2011a; Taylor *et al.*, 2018), with the World Health Organization recommending its removal from international drug control treaties (World Health Organisation, 2017), relatively little is known about CBD’s effects on cognitive and psychomotor function, including whether it influences one’s ability to safely operate a motor vehicle.

Epidemiological evidence suggests that cannabis intoxication is associated with a modestly increased risk of involvement in a road traffic crash in which the cannabis user is culpable (Rogeberg & Elvik, 2016; Rogeberg & Elvik, 2017). Controlled, experimental studies using simulated and on-road assessment techniques have likewise demonstrated that recent cannabis use can influence fundamental driving skills (e.g. lateral and longitudinal vehicular control) (Anderson *et al.*, 2010; Arkell *et al.*, 2019b; Bosker *et al.*, 2012; Downey *et al.*, 2013; Hartley *et al.*, 2019; Hartman *et al.*, 2015, 2016; Lenne *et al.*, 2010; Micallef *et al.*, 2018; Papafotiou, Carter, & Stough, 2005; Veldstra *et al.*, 2015). These effects are likely a result of Δ^9 -THC acting on the major central nervous system endocannabinoid system

receptor, cannabinoid receptor 1 (CB₁R), inducing intoxication (e.g. cognitive and psychomotor impairment, sedation) (Boggs *et al.*, 2018a).

Unlike Δ^9 -THC, CBD does not directly activate CB₁R (Ibeas *et al.*, 2015). Thus, while some research suggests the cannabinoid may exacerbate Δ^9 -THC-induced driving impairment (Arkell *et al.*, 2019b), this effect has been attributed to CBD blocking Δ^9 -THC degradation (e.g. via inhibition of cytochrome [CYP] 3A4, CYP2C9, CYP2C19) (Yamaori *et al.*, 2011), rather than inducing intoxication *per se* (Arkell *et al.*, 2019b). Other studies have likewise shown that CBD (alone) (200–900 mg, p.o.; 15–60 mg inhaled) does not influence cognitive performance on discrete neuropsychological tests (Arndt & de Wit, 2017; Bhattacharyya *et al.*, 2009; Birnbaum *et al.*, 2019; Borgwardt *et al.*, 2008; Dalton *et al.*, 1976; Fusar-Poli *et al.*, 2009; Hindocha *et al.*, 2015; Hundal *et al.*, 2017; Karniol *et al.*, 1974; Leweke *et al.*, 2000) or induce somnolence (750–6000 mg, p.o.) (Taylor *et al.*, 2018), unless perhaps co-administered with certain sedating medications (e.g. clobazam) (Anderson *et al.*, 2019; Geffrey *et al.*, 2015; Morrison *et al.*, 2019). In fact, findings from some preclinical studies suggest that low doses of CBD could be “wake-inducing” and may have utility in the treatment of excessive daytime sleepiness (Monti, 1977; Murillo-Rodríguez *et al.*, 2006; Yi *et al.*, 2008). Nonetheless, it is important to recognise that driving is a complex task requiring high levels of vigilance so may be particularly susceptible to the impairing effects of psychoactive drugs. Confirmation of CBD’s precise effects on driving performance is therefore warranted.

One additional issue with CBD and driving is the potential for false positives in roadside (mobile) drug testing. CBD has a similar chemical structure to Δ^9 -THC rendering it plausible that it may be mistakenly identified as Δ^9 -THC on tests relying on specific molecular features. *In vitro* studies have also shown that CBD can undergo bioconversion to Δ^9 -THC under simulated physiological conditions (Merrick *et al.*, 2016; Watanabe *et al.*, 2007), although this effect has not yet been observed *in vivo* (Wray *et al.*, 2017). In the state of New South Wales (NSW), Australia, roadside drug testing involves an initial test for oral fluid Δ^9 -THC using the Securetec DrugWipe[®] (DW) device; if positive, a second test is performed using the Dräger DrugTest[®] 5000 (DT5000). If both tests yield positive results, confirmatory analyses are performed using mass spectrometry. These two point-of-collection testing (POCT) testing devices, which use enzyme-linked immunosorbent assay technology, are reported to have poor sensitivity to Δ^9 -THC (Arkell *et al.*, 2019a; Wille *et al.*, 2015); however, their ability to distinguish between different cannabinoids is not well characterised.

The primary aim of this study is to investigate the effect of acute, oral CBD treatment, at doses spanning the nutraceutical and pharmaceutical range (15, 300 and 1500 mg), on simulated car driving performance as well as discrete cognitive skills related to driving and subjective feelings of intoxication. We hypothesise that CBD will not affect simulated driving or cognitive performance. A secondary aim will be to determine if potentially unimpaired CBD users are at risk of testing “false-positive” to Δ^9 -THC in standard POCT roadside drug tests.

2.0 Methods

2.1 Study Design and Participant Population

2.1.1 Study Design

The study is a randomised, double-blind, placebo-controlled, crossover, dose-ranging, non-inferiority trial investigating the effect of acute, oral CBD treatment on simulated car driving performance. Participants will complete four separate research sessions involving two 30-minute simulated driving tests; the first 45- and the second 210-minutes following oral ingestion of placebo, or 15, 300, or 1500 mg CBD. All sessions will be separated by a washout period ≥ 7 days. The trial will be conducted at the Woolcock Institute of Medical Research, Sydney, Australia and sponsored by the University of Sydney. The design has been approved by the Human Research Ethics Committee (HREC) of the University of Sydney (2019/474) and registered on the Australia and New Zealand Clinical Trials Registry (ACTRN12619001552178). The project is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research.

2.1.2 Inclusion Criteria

Eligible participants will: (a) be healthy males and females aged between 18–65 y; (b) have held a full (unrestricted) Australian driver’s license for ≥ 1 y (i.e. have ≥ 4 y of unsupervised driving experience); (c) not have used cannabis in the previous 3 months (confirmed by a negative urine drug screen at the medical screening); and (d) be proficient in English and able to provide informed consent. For the purpose of this trial, ‘healthy’ has been defined as the absence of an uncontrolled, physical health problem; specific criteria for psychiatric conditions are set out below.

2.1.3 Exclusion Criteria

The following exclusion criteria will be applied:

- (a) Cannabis dependence or any other drug or alcohol dependence, as per the International Statistical Classification of Diseases 10th Revision (ICD)-10 criteria (World Health Organisation, 2010) or at the medical officer's discretion;
- (b) Contraindications to cannabinoids, including a clinically significant prior adverse response to cannabis, cannabinoid products or synthetic cannabinoids;
- (c) History of a major psychiatric disorder within the previous 12 months (except clinically-managed mild depression or anxiety) as per the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria (American Psychiatric Association, 2013) or at the medical officer's discretion;
- (d) History of attempted suicide or current suicide ideation as determined by a score >0 on Question 9 of the Patient Health Questionnaire (PHQ)-9 (Kroenke, Spitzer, & Williams, 2001);
- (e) A diagnosed sleep disorder, as per the International Classification of Sleep Disorders Diagnostic and Coding manual (Sateia, 2014) or at the medical officer's discretion;
- (f) Pregnant or lactating. All female volunteers of childbearing potential will be required to complete a human chorionic gonadotrophin (hCG) urine screen to rule out pregnancy. Females of childbearing potential and males with a female partner must agree to use a reliable form of contraception during and one month following their participation in this project;
- (g) Inability to refrain from alcohol consumption 24 h prior to each experimental trial;
- (h) Inability to refrain from using other central nervous system active drugs (e.g. cannabis, opioids, benzodiazepines) while participating in this project;
- (i) Use of medications that may influence CBD metabolism (e.g. inducers or inhibitors of the CYP450 enzyme system);
- (j) Use of medications handled by transporter proteins or CYP enzymes that are inhibited by CBD, such as anticoagulants, calcium channel blockers, beta blockers and sulfonylureas;
- (k) Use of anticonvulsant medications (e.g. clobazam or valproate);
- (l) Required to complete mandatory drug testing for cannabis (e.g. workplace testing);
- (m) High likelihood of experiencing driving simulator sickness, as determined at the medical screening using the Simulator Sickness Questionnaire (SSQ) (Kennedy *et al.*, 1993);

- (n) High habitual caffeine intake (i.e. $>300 \text{ mg}\cdot\text{d}^{-1}$); and
- (o) A body mass index (BMI) $>30 \text{ kg}\cdot\text{m}^2$.

2.1.4 Recruitment Strategies

Participants will be recruited via word-of-mouth and using a general advertisement (Supplementary File 1) published in print and online media, emailed to individuals who have previously registered their interest in participating in clinical trials with the Lambert Initiative for Cannabinoid Therapeutics, and displayed around the local University area.

Participants will be reimbursed for any expenses incurred as a result of study participation up to a value of AU\$60 per research session. They will also receive AU\$480 to recompense them for their time. If an individual discontinues their participation, they will be reimbursed for the components of the study they completed (i.e. AU\$120 per attendance).

2.1.5 Telephone and Online Participant Screening

The online study advertisement will be linked to a participant screening survey (REDCapTM, v8.3.1) which will prompt volunteers to answer a series of 'Yes-No' questions intended to provide an initial indication of their suitability to participate (see: <https://redcap.sydney.edu.au/surveys/?s=7FETKYATY9> and Supplementary File 2).

Volunteers who may be suitable to participate will be invited to provide their contact details. Individuals who provide their contact details or who contact the research team directly will then complete a telephone interview with clinical trial coordinator before scheduling a formal onsite screening visit.

2.1.6 Eligibility Screening Procedures

Volunteers will complete a formal onsite eligibility screen with the trial coordinator and a medical officer. Initially, they will be informed of the study requirements and risks before providing written informed consent in accordance with the principles of the Helsinki Declaration (1983). Eligibility will then be assessed using the above criteria. Individuals will undergo a medical and psychiatric evaluation; complete a urine drug screen (DrugCheck Nx[®] Step Onsite Drug Test, Minnesota, USA) to identify recent use of cannabis and, if they are female, a hCG urine screen (AlereTM hCG Combo Cassette, Massachusetts, USA); have their height and weight measured to determine BMI; and complete a 30-minute practice drive on the simulator (i.e. the full driving test) to become familiar with the simulated environment,

and to reduce practice effects (Irwin *et al.*, 2013). Finally, the medical officer will write each eligible participant a prescription for the trial medication.

2.1.7 Randomisation

Participants will be assigned to one of four possible treatment orders using a pre-populated randomisation schedule. The four treatment orders will constitute a Latin square and the schedule will be randomly generated in three balanced blocks of eight and one block of six (in which each sequence appears at least once but no more than twice) by an independent statistician using SAS (v9.4, Cary, NC). Randomisation will not be stratified. As this is a blinded study, the participant and outcome assessor(s) will not be aware of the treatment order; this will only be known to the statistician and those individuals involved in treatment preparation, none of whom will have contact with participants.

2.2 Study Treatments

Four different treatments will be investigated: (1) Placebo (0 mg CBD); (2) Low Dose CBD (15 mg); (3) Moderate Dose CBD (300 mg); and (4) High Dose CBD (1500 mg). The Low Dose was chosen to mirror that of popular nutraceutical products available overseas and online, such as NuLeaf (e.g. $\sim 50 \text{ mg}\cdot\text{mL}^{-1}$; nuleafnaturals.com/); AnandaHemp (e.g. $\sim 10\text{--}20 \text{ mg}\cdot\text{mL}^{-1}$; anandahemp.com/) and Populum (e.g. $\sim 8 \text{ mg}\cdot\text{mL}^{-1}$; populum.com); whereas the Moderate and High Doses were chosen to reflect the ‘lower’ and ‘upper’ dosages used in clinical trials for a variety of indications (Lattanzi *et al.*, 2018).

The investigational product (GD Cann[®]-C; GD Pharma Pty Ltd, Norwood, South Australia, Australia) is an oral formulation containing synthetic CBD ($100 \text{ mg}\cdot\text{mL}^{-1}$) in medium chain triglyceride (MCT) oil. The placebo will be MCT oil. Neither product will contain any other minor cannabinoids or terpenes/terpenoids.

2.2.1 Treatment Preparation

The active CBD oil will be delivered in volumes of 150 μL , 3.0 mL and 15.0 mL. To aid blinding, each dose will be made up to a total volume of 15 mL via the addition of placebo oil. This process will be completed by a trained, unblinded drug dispenser (under the authority of a medical officer) ~ 15 min prior to administration; a witness will be present to observe and verify the procedure. Study personnel involved in treatment preparation will not have any contact with participants. The total volume of oil (15 mL) will be added to a high fat dietary supplement (100 mL; 50 g fat) (Calogen[®], Nutricia, Macquarie Park, Australia).

This approach was selected as pharmacokinetic data suggest that plasma concentrations of CBD are greatly increased when it is co-ingested with a high fat meal (Birnbaum et al., 2019; Taylor et al., 2018). A blinded investigator will then collect the prepared treatment from the drug storage unit and confirm it is labelled with the correct identification code before administration to the study participant. The blinded study investigator will instruct and directly observe the participant to orally ingest the prepared treatment.

2.3 Study Procedures

Participants will complete four research sessions separated by a washout period ≥ 7 days within a maximum of 60 days. Individuals will be instructed to maintain their usual diet and physical activity patterns and to avoid using illicit drugs (including cannabis) while participating in this trial.

2.3.1 Pre-Trial Procedures

Prior to each session, participants will be instructed to: (1) abstain from alcohol (≥ 24 h) and caffeine-containing foods and beverages (≥ 12 h); (2) keep a written record of all foods and beverages consumed (24 h); (3) spend ≥ 8 h in bed overnight; and (4) arrive at the laboratory fasted (~ 10 h) and well-hydrated between 07:00–09:00. Participants will receive a copy of their pre-trial diet record after the initial session and be instructed to replicate their dietary behaviour ahead of each subsequent session.

2.3.2 Experimental Procedures

Participants will arrive at the laboratory fasted between 07:00–09:00 and complete breathalyser and UDS tests to confirm they are drug (i.e. cannabis, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine and opiates) and alcohol-free; females of childbearing potential will also complete hCG screens. Trials will be discontinued in the event of a positive test result. The urine sample will also be used to assess hydration status (Urine Specific Gravity [U_{SG}]; Palette Digital Refractometer, ATAGO, USA) as mild hypohydration may impair cognitive function (McCartney, Desbrow, & Irwin, 2017) and simulated driving performance (Watson *et al.*, 2015). If U_{SG} is >1.024 , likely indicating hypohydration (Armstrong *et al.*, 2010), participants will be required to consume a bolus of water (~ 500 mL) and collect a second urine sample to reassess U_{SG} ~ 30 min later. This procedure will be repeated if required until a U_{SG} value below the accepted threshold is obtained. Once euhydration has been verified, participants will re-familiarise themselves with

the driving simulator and cognitive tests before completing a series of baseline assessments (Table 1). They will then be administered a standardised breakfast meal consisting of toasted bread (Wonder White[®], Goodman Fielder) and their preferred spread(s) (e.g. margarine, jam) followed by their assigned treatment.

Participants will complete two 30-minute simulated driving performance tests at each research session; the first 45- and the second 210-minutes post-treatment. The timing of the second driving test is based on pharmacokinetic data indicating that time to C_{max} for 1500 mg orally ingested CBD is ~4 hours (Taylor et al., 2018). Other measures will also be taken at regular intervals (Table 1). A standardised snack will be provided 150-minutes post-treatment. Participants will rest quietly in between assessments. At the conclusion of each session, participants will complete an adverse events checklist and indicate which treatment they think they received.

2.3.3 Data Collection

All assessments will be completed as per the timeline indicated in Table 1.

2.3.3a Simulated Car Driving Performance

Simulated car driving performance will be measured on a custom-built, computerised, fixed-base simulator (SCANeR studio simulation engine, v1.6r85, OKTAL, Paris, France) equipped with original vehicle controls (accelerator and brake pedals, steering wheel, seat, safety belt, indicator, automatic gear shift, and hand brake) linked to dedicated graphics computer equipment. Visual images will be displayed on three 32-inch LCD monitors set to provide a 100° field of view. Images from the simulation software will refresh at a rate of 60 Hz and data will be sampled at a rate of 20 Hz. Speed will be displayed on a digital dashboard. Surround sound will provide auditory feedback and force feedback steering will provide haptic feedback. The scenario is a realistic and complex drive that incorporates highway, town and rural segments and has previously demonstrated sensitivity to the impairing effects of Δ^9 -THC (Arkell et al., 2019b). It commences with a ~7 minute “car following” task during which participants follow a lead vehicle programmed to accelerate and decelerate at 30 second intervals in a sinusoidal manner (i.e. between 90 and 110 km·h⁻¹). Individuals will be instructed to maintain what they believe is a safe distance headway. The task occurs on a two-lane, dual-carriageway highway in steady traffic. Outcome measures for this segment will be standard deviation of lateral position (SDLP) (see 2.3.4 *Primary Outcome Measure*), mean distance headway and standard deviation of distance headway

(SDDH). Headway outcomes should provide an indication of participants' perceived level of impairment (i.e. their confidence to detect and react to the lead vehicle's speed changes without risking a collision). The car following segment is followed by a 25-minute drive that includes both highway (i.e. two-lane, dual-carriageway roads with fixed posted speed limits of 110 km·h⁻¹) and rural (i.e. winding single-lane roads with variable posted speed limits of between 60 and 100 km·h⁻¹) roads. Outcome measures for this segment will be SDLP, mean speed and standard deviation of speed (SDSP). Participants will be instructed to follow all road rules, keep to the posted speed limits and drive in the centre of their lane at all times. They will also be instructed to concentrate and drive to the best of their ability. The SSQ (Kennedy et al., 1993) will be administered following each drive to identify cases of simulator sickness.

2.3.3b Cognitive Function

Participants will complete three computerised cognitive tests that have previously demonstrated sensitivity to the impairing effects of Δ^9 -THC (Arkell et al., 2019b; Vandrey *et al.*, 2017).

During the Digit Symbol Substitution Test, participants are presented with a series of geometric patterns labelled 1–9, each consisting of an array of filled and blank squares in a 3 × 3 grid (McLeod *et al.*, 1982). When a number appears in the middle of the screen, participants are instructed to replicate the pattern corresponding to that array using the numeric keypad of a computer keyboard. Participants have 90 s to replicate as many patterns as possible. Outcome measures are number of correct patterns and pattern accuracy.

During the Paced Auditory Serial Addition Test (~3 minutes), participants watch single digits appear on a screen and are instructed to sum each new digit with the preceding one (Herrmann *et al.*, 2015). They respond by clicking on the correct answer from a list of numbers presented on the screen. Outcome measures are median response time and the total number of correct trials.

During the Divided Attention Test (~4 minutes), participants must track a horizontally moving stimulus on the screen using their mouse while simultaneously responding to peripheral visual stimuli by clicking the left mouse button whenever a number in any corner of the screen matches a target number presented at the bottom of the screen (Kleykamp, Griffiths, & Mintzer, 2010). Outcome measures are the mean distance of the cursor from the target (tracking error), the number of target numbers correctly identified and response time.

2.3.3c Psychomotor Vigilance

The psychomotor vigilance test (PVT) device is a hand-held box that emits a red light at random intervals between 2 and 10 seconds (PVT-192, Ambulatory Monitoring Inc, Adaley, NY, USA). Participants will be instructed to respond to the light quickly as possible during each 10-minute test. The outcome variables to be analysed will be median reaction time and number of lapses (>500 ms). The ex-Gaussian distribution parameters: (1) μ , the mean and (2) σ , the standard deviation (SD) of the Gaussian (normal) component (i.e. fastest reaction times) and, (3) τ , the mean and SD of the exponential component (i.e. the degree of positive skew) (Whelan, 2008) will also be determined using the using the quartile maximum likelihood estimation procedure in QMPE 2.18 (Cousineau, Brown, & Heathcote, 2004).

2.3.3d Cognitive and Psychomotor Impairment

The DRUID[®] (Version 2.0) is a computerised application ('app') that has been designed to measure cognitive and behavioural impairment following the use of drugs and/or alcohol. The app requires users to complete four discrete tests that measure divided attention, decision making, reaction time, motor tracking and balance performance on a tablet device (iPad, Apple[®], Cupertino, USA). The tests (~2 minutes in total) are detailed elsewhere (Richman, 2019). Once testing is complete, the DRUID[®] app generates an overall impairment score between 0 and 100. Research has shown that the app is sensitive to the impairing effects of other sedative drugs and is a candidate rapid screening test for identifying intoxicated drivers (Richman, 2019).

2.3.3e State Anxiety

The short-form STAI-S (Marteau & Bekker, 1992; Spielberger, 1983) is a 6-item questionnaire that requires respondents to indicate how calm, tense, upset, relaxed, content and worried they feel on a scale of 1–4, where 1 is "not at all" and 4 is "very much". After reversing the scores on "positive" items, the total score is summed and multiplied by 20/6 to provide result comparable to that obtained on the 20-item STAI-S.

2.3.3f Driving Self-Efficacy

The Adelaide Driving Self Efficacy Scale (ADSES) (George, Clark, & Crotty, 2007) is a 12-item questionnaire that requires respondents to indicate their confidence in their ability to

safely operate a motor vehicle under various conditions (e.g. in heavy traffic) on a scale of 0–10, where 0 is “not confident” and 10 is “completely confident”. Summed scores provide an indication of driving self-efficacy, or an individuals’ perception of their own driving ability.

2.3.3g Heart Rate (HR) and Blood Pressure (BP)

Seated heart rate and blood pressure (BP) will be measured using an automated sphygmomanometer. Measures will be taken in duplicate, or triplicate if BP values differ by >15 mmHg (Griffin, Robergs, & Heyward, 1997), using the right arm, and averaged.

2.3.3h Subjective Drug Effects

Visual analog scales (VAS) will be used to measure subjective drug effects (i.e. feeling stoned, sedated, alert, anxious, sleepy). Measures will be completed on 100 mm scales, where 0 is “not at all” and 100 is “extremely”.

2.3.3.i Blood Sampling

Venous blood samples will be drawn into 10 mL pre-treated EDTA vacutainers (Becton, Dickinson and Company, Franklin Lakes, NJ) from a cannula (or needle) inserted into an accessible forearm vein and centrifuged at 1500 x g for 15 min at 4°C on collection. Aliquots of plasma supernatant will be stored in 1.5 mL Eppendorf tubes at –80°C and later analysed via liquid chromatography-tandem mass spectrometry (LC-MS/MS) according to established protocols (Arkell et al., 2019b) to determine plasma concentrations of endocannabinoids, cannabinoids and their metabolites.

2.3.3.j Standard Roadside Drug Tests and Saliva Sampling

Oral fluid tests will be performed using the DrugWipe® 5S (Securetec, Neubiberg, Germany) (DW) and Dräger DrugTest® 5000 (Dräger, Lübeck, Germany) (DT5000) devices. The details of these devices, including a thorough description of the testing procedures, can be found elsewhere (Arkell et al., 2019a). Briefly, participants will be instructed to wipe the DW collection pad down the centre of their tongue; if sufficient fluid is collected (~10–20 µL), the device will be held vertically for 10 seconds before being left to rest in a horizontal position for 8 minutes to generate a qualitative result. Testing on the DT5000 will require participants to move the collecting device back and forth between their cheek and gums until the end of the sampling is signalled by a blue discoloration of the collection pad. The investigator will then insert the sample into the DT5000 device for analysis. To maintain the blind, neither the

participant nor the outcome assessor(s) will be informed of the test results, which will be recorded by an unblinded investigator (e.g. an individual involved in treatment preparation) who will not have any contact with participants. In addition to these drug tests, participants will also be required to collect an oral fluid sample using the Quantisal™ collection device (Immunoanalysis, Pomona, CA, USA). Briefly, the device will be placed under the participant's tongue until the indicator turns blue and placed into the stabilizing buffer. Samples will be stored at 4°C and analysed within one month of collection via LC-MS/MS according to established protocols (Arkell et al., 2019a) to determine oral fluid cannabinoid concentrations (Lee *et al.*, 2012). Food and fluid will be disallowed for 10 min prior to each set of oral fluid tests. The results of the DW and DT500 tests will be classified as *true positive*, *true negative*, *false positive* or *false negative*, based on the LC-MS/MS quantified oral fluid Δ^9 -THC concentration.

2.3.4 Primary Outcome Measure

The primary outcome measure in this investigation will be SDLP on the simulated driving performance tests. SDLP has been shown to increase dose-dependently with the administration of sedative drugs (e.g. alcohol, Δ^9 -THC, benzodiazepines) (Dassanayake *et al.*, 2011; Irwin *et al.*, 2017; Veldstra et al., 2015). These changes in SDLP correlate reasonably with epidemiological data on the risk of road traffic crashes with various psychoactive agents (Owens & Ramaekers, 2009), although more direct evidence to support a relationship between SDLP and the risk of road traffic crashes is still required.

2.4 Statistical Methods

2.4.1 Defining the Non-inferiority Margin

This trial will test the specific hypothesis that CBD is not “inferior” to- (i.e., *more impairing than-*) placebo by more than the *non-inferiority margin*, Δ , i.e. the smallest meaningful decrement in simulated driving performance, or the minimum amount of impairment required to increase a driver's risk of crashing (Quertemont, 2011). We propose that this impairment occurs at the level of the legal blood alcohol concentration (BAC) limit (i.e. 50 mg·dL⁻¹ in Australia), since lower BACs are rarely implicated in road traffic crashes (i.e. <0.1% of all incidents) (Centre for Road Safety NSW, 2016) and we have therefore defined Δ as the Cohen's d_z effect of 0.05% BAC on SDLP.

The following methods were used to quantify Δ . Initially, data from the four studies known to have investigated the effect of acute alcohol intoxication on simulated driving performance (SDLP) using a dose-ranging experimental design and a placebo control were extracted (Table 2). Where SDLP was measured more than once at a given BAC (e.g. in different sections of a driving task, such as a ‘winding timbered road’, ‘vigilance section’, ‘simple route’) (Berthelon & Gineyt, 2014; Kenntner-Mabiala *et al.*, 2015), only those data collected during controlled highway driving tasks (i.e. comparable to that being used in the current study) were included. Within-subject Cohen’s d_z effect sizes were calculated for each comparison using the spreadsheet by Lakens (2013) and assuming a correlation co-efficient (R) of 0.55, as per a previous meta-analysis (Irwin *et al.*, 2017) (Table 2). Each Cohen’s d_z effect was then correlated against ‘Actual BAC’ (defined in Table 2). The resulting linear equation (Equation 1) predicts a Cohen’s d_z effect (or Δ) of 0.50 at 0.05% BAC.

$$\text{Equation 1: } \text{Cohen's } d_z = (12.429 \times \text{BAC [\%]}) - 0.124$$

This Δ was used calculate the target sample size. Using a power ($1-\beta$) of 0.80, a one-sided $\alpha=0.05$ and an equivalent effect (Cohen’s $d_z=0.50$), we predict that 27 participants will be required to demonstrate non-inferiority of CBD. Thirty individuals will therefore be recruited and randomised to account for attrition.

2.4.2 Statistical Analysis Plan

The current trial will test the hypothesis that CBD, at doses of 15, 300 and 1500 mg, has no meaningful impact on simulated driving performance. Non-inferiority will be established at the one-sided α significance level, if the upper limit of the 95% confidence interval (CI) for the Cohen’s d_z effect of each respective CBD treatment (at each measured timepoint) on SDLP does not cross Δ (Figure 1). Within-subject Cohen’s d_z effects will be calculated via standard methods (Lakens, 2013) and their associated 95% CIs will be derived using the following equations (Borenstein *et al.*, 2009):

$$\text{Equation 2: } V_d = \left(\frac{1}{n} + \frac{d^2}{2n} \right) \times 2 \times (1 - R)$$

$$\text{Equation 3: } SE_d = \sqrt{V_d}$$

$$\text{Equation 4: } 95\% \text{ CI's} = d \pm SE_d \times 1.96$$

Where V_d is the variance of Cohen's d_z , d is Cohen's d_z , n is the sample size, R is the correlation co-efficient and SE_d is the standard error of Cohen's d_z .

Any CBD treatment that is found to be either '*non-inferior*' (i.e. and therefore, potentially *superior*) or '*not non-inferior*' (i.e. and therefore, potentially *inferior*) to placebo in terms of its effect on SDLP (see examples in Figure 1) at a given timepoint will also be subjected to a secondary, superiority analysis at the two-sided α significance level using a paired t -test. These analyses will be completed using SPSS Statistics (IBM Corp. 2012, Armonk, N.Y., USA). Each secondary outcome variable will likewise be analysed using traditional superiority methods at the two-sided α significance level as in previous studies (Lanz *et al.*, 2019). Effect sizes will be calculated as partial eta squared (η_p^2) and Cohen's d_z , where appropriate. There are no interim analyses planned for this study. The final decision to terminate the trial lies with the principal investigator and will be based on safety data and target sample size.

[INSERT FIGURE 1 HERE]

2.4.3 Data Management

All data and information obtained for the purpose of this research that could identify participants will be treated as confidential and stored securely, according to Good Clinical Practice and HREC requirements. Participant data will be identified by a unique code allocated at the time of consent. The key linking the participant's identity and personal details to the relevant code will be stored on a password-protected file that will not be accessible from the internet. All hard files will be stored securely at the study site. Electronic data will be entered into a secure electronic data capture system (REDCapTM, v8.3.1). Public access to datasets generated from the study will be available on reasonable request to suitably qualified researchers with a legitimate analysis proposal. Only researchers affiliated with the study will have access to participant data.

3.0 Comment

While cannabis intoxication has been associated with a modestly increased risk of involvement in a road traffic crash (Rogeberg & Elvik, 2016; Rogeberg & Elvik, 2017), the

extent to which CBD influences one's ability to safely operate a motor vehicle is in need of clarification. Hence, the current trial will investigate the impact of acute, oral CBD treatment on simulated car driving performance. Participants will also be subjected to standard NSW roadside drug testing procedures to determine if potentially unimpaired CBD users are at risk of giving a "false-positive" test to Δ^9 -THC using POCT devices.

The trial has been designed with the intent to maximise ecological validity and generalisability, while maintaining a high degree of scientific rigor and experimental control, and thus, the sensitivity to detect small changes in simulated driving performance. In fact, it intends to reflect a "typical day", during which an individual takes their medication (or 'supplement') with breakfast, before driving to work, school or other. An orally administered oil was selected as the investigational product given that these are commonly used in medications (e.g. Epidiolex[®]) and by non-clinical populations (Bonn-Miller et al., 2017). The different doses were likewise chosen to span the nutraceutical and pharmaceutical range. Hence, we expect our findings will be (broadly) applicable to a variety of real-life contexts.

Of course, CBD may still exert different effects in certain populations. For instance, individuals using sedative drugs that are metabolised by CYP enzymes inhibited by CBD (e.g. clobazam, Δ^9 -THC) may experience increased psychomotor impairment and drowsiness (i.e. due to a delay in the degradation of these other medicines), and thus, impaired driving performance (Anderson et al., 2019; Geffrey et al., 2015; Morrison et al., 2019). In contrast, individuals using CBD to ameliorate symptoms that themselves impair driving performance (e.g. chronic pain), could potentially experience an improvement (Arnell et al., 2019b; Jamison *et al.*, 2003; Lorenz, Beck, & Bromm, 1997). However, it is important to understand the effects of CBD in individuals with no underlying health conditions before considering these interactions.

One potential limitation of the current trial is that it only assesses the impact of acute CBD treatment while most individuals will be using CBD chronically. Of note, however, is that chronic dosing at 1500 mg·d⁻¹ (i.e. the highest level that has so far been studied) has been reported to produce peak plasma CBD concentrations similar to those observed when an equivalent acute dose is co-ingested with a high fat meal (i.e. ~1600 vs. 1400 ng·mL⁻¹, respectively), as will be the case in the current trial (Taylor et al., 2018). Hence, we would not expect chronic dosing to yield vastly different results. An additional point to note is that the current protocol does incorporate a number of different assessments. While the majority

of these are quite brief and are not expected to overwhelm participants, results may need to be interpreted with some consideration for the influence of fatigue.

Another feature of the current trial is its non-inferiority design; that is, unlike many studies in which the objective is to demonstrate that two or more treatments differ in their effect, this investigation will test the hypothesis that CBD is not “inferior” to— (i.e., *more impairing than*—) placebo by more than the *non-inferiority margin*, Δ . Here, Δ has been set at Cohen’s $d_z=0.50$ (on SDLP). This value was selected on the basis that: (1) Δ should reflect the smallest meaningful level of impairment; and (2) data from several comprehensive, dose-ranging studies suggest that a BAC of $50 \text{ mg}\cdot\text{dL}^{-1}$ has an effect of this magnitude on a ~15–60 minute simulated highway driving test (Berthelon & Gineyt, 2014; Kenntner-Mabiala et al., 2015; Mets *et al.*, 2011; Veldstra *et al.*, 2012). Of course, it is important to acknowledge that, although “tolerated” in many countries (Furtwaengler & de Visser, 2013), this level of impairment (i.e. at 0.05%BAC) is not insignificant and any substance or behaviour that elicits a comparable effect should still be recognised as potentially hazardous. Other considerations include the fact that drug-induced changes in SDLP may fluctuate in size depending on the experimental context (e.g. the specific driving test, participant population) (Irwin et al., 2017) and that the current method assumes that if CBD is impairing, it will affect lateral control in a similar manner to other drugs (e.g. alcohol, Δ^9 -THC, benzodiazepines) (Dassanayake et al., 2011; Irwin et al., 2017; Veldstra et al., 2015). It is also possible that even though CBD might not have a “meaningful” impact on car driving performance, CBD coupled with other factors (e.g. fatigue, distraction) could have a detrimental effect that exceeds the non-inferiority margin. Thus, results will need to be interpreted with some degree of caution (as is the case with any non-inferiority trial).

This research will yield original findings with important practical applications. To date, no published studies have described the effect of CBD alone on car driving performance and relatively few have examined its impact on other discrete driving-related ‘skills’ (e.g. cognitive function, alertness). Results may aid in the development of patient and/or user guidelines, as well as drug-driving legislation that ensures the safe use of CBD by drivers.

Figure Captions

Figure 1. Potential outcomes of the current non-inferiority trial. Δ : Non-inferiority Margin; SDLP: Standard Deviation of Lane Position. Positive Cohen's d_z values indicate an increase in SDLP (compared to placebo), and therefore, a decrement in simulated driving performance, whereas negative Cohen's d_z values reflect a decrease in SDLP (compared to placebo), and therefore, improvement in simulated driving performance. Any CBD treatment that is found to be either '*non-inferior*' (i.e. and therefore, potentially *superior*) or '*not non-inferior*' (i.e. and therefore, potentially *inferior*) to placebo in terms of its effect on SDLP at a given timepoint will also be subjected to a secondary, superiority analysis.

Tables

Table 1. A summary of the assessments completed throughout the investigation

Measure (Ordered from First to Last)	Screening	Research Sessions (× 4)										
		Baseline (-60 min)		Pre-DS I (15-45 min)		Post-DS I (75-95 min)		'Halfway' (140-150 min)		Pre-DS II (180-210 min)		Post-DS II (240-260 min)
Cannabis Use Hx	•											
Driving Hx	•											
Height and BM	•											
UDS	•	•										
hCG Screen	•	•										
U _{SG}		•										
HR & BP		•	Breakfast (-15-0 min)	•		•		•		•		•
STAI-S		•		•		•		•		•		•
VAS		•	Tx (0 min)	•		•		•		•		•
DRUID® Test		•		•	DS I (45-75 min)				Rest (150-180 min)	•		
OF Sampling		•		•				•		•		
DW		•	Rest (0-15 min)	•				•		•		
DT5000		•		•				•		•		
DSST		•		•						•		
DAT		•		•						•		
PASAT		•		•						•		
Blood Sampling		•		•		•				•		•
ASEDS				•						•		
SSQ						•						•
PVT						•						•
AE Checklist												•

AE: Adverse Event; ASEDS: Adelaide Driving Self Efficacy Scale; BM: Body Mass; BP: Blood Pressure; BrAC: Breath Alcohol Concentration; DAT: Divided Attention Test; DS: Driving Simulation; DSST: Digit Symbol Substitution Test; DT5000: Dräger DrugTest® 5000; DW: Securetec DrugWipe®; hCG: human chorionic gonadotrophin; HR: Heart Rate; Hx: History; OF: Oral Fluid; PASAT: Paced Auditory Serial Addition Test; PVT: Psychomotor Vigilance Test; SSQ: Simulator Sickness Questionnaire; STAI-S: State and Trait Anxiety Inventory; Tx: Treatment Administration; UDS: Urine Drug Screen; U_{SG}: Urine Specific Gravity; VAS: Visual Analog Scales (Subjective Drug Effects).

Table 2. Results of studies investigating the effect of acute alcohol intoxication on simulated car driving performance (SDLP) using dose-ranging experimental designs.

Citation	Driving Task	Target BAC (%)	Actual BAC (%)	Sample Size (<i>n</i>)	Placebo SDLP (cm)		Alcohol SDLP (cm)		ES
					Mean	SD	Mean	SD	
‡Berthelon & Gineyt (2014)	30 km HWY drive at 110 km·h ⁻¹ .	(a) 0.03	0.028	16	26.4	6.8	25.9	7.2	-0.08
		(b) 0.05	0.051	16	26.4	6.8	28.4	6.8	0.31
		(c) 0.08	0.080	16	26.4	6.8	31.9	8.7	0.73
Veldstra et al., (2012)	22.6-km rural drive at 100 km·h ⁻¹ .	(a) 0.03	0.023	17	15.8	4.0	17.7	4.0	0.50
		(b) 0.05	0.049	17	15.8	4.0	17.9	4.0	0.55
		(c) 0.08	0.080	17	15.8	4.0	19.9	4.0	1.08
Mets et al., (2011)	100-km HWY drive at 95 km·h ⁻¹ .	(a) 0.05	0.042	27	28.0	6.5	29.7	7.1	0.26
		(b) 0.08	0.072	27	28.0	6.5	33.8	7.2	0.89
		(c) 0.11	0.100	27	28.0	6.5	36.3	9.8	1.00
†Kenntner-Mabiala et al., (2015)	48 km HWY drive following a lead vehicle traveling between 85 and 90 km·h ⁻¹ .	(a) 0.05	0.051	24	20.0	5.0	23.0	6.0	0.57
		(b) 0.08	0.078	24	20.0	5.0	25.0	6.0	0.94

BAC: Blood Alcohol Concentration; ES: Cohen's d_z Effect Size; HWY: Highway; SD: Standard Deviation; SDLP: Standard Deviation of Lateral Position. Actual BAC: Calculated as the average of the measured pre- and post-drive BAC concentrations, except in the case of Veldstra et al., (2012) where BAC was measured pre-drive, only. †, SDLP was also measured on a 5 km winding road (80 km·h⁻¹) and 2 km rural road; ‡, SDLP was also measured on a 10 min drive following a lead vehicle (between 70 and 90 km·h⁻¹).

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